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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/531,385	GRUS ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12-15 and 19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment, filed 8/30/06, is acknowledged and has been entered. Claims 1-2, 10, and 16-18 were amended. Claims 1-26 are pending in the application, with claims 12-15 and 19-26 currently withdrawn.

Objections/Rejections Withdrawn

2. The objections to claims 1, 10, and 17-18 are withdrawn in response to the amendments.

3. The rejections under 35 USC 112, 2nd paragraph not reiterated below have been withdrawn in response to the amendments.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-11 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 recites that "if the pattern of said individual is **more related** to the pattern of glaucoma patients than to the pattern of healthy individuals, glaucoma is diagnosed". The term "more related" is indefinite because the term not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear by what standard patterns

would be considered to be "more related" to each other in the absence of a definition for this term in the specification. It is also unclear to what extent patterns may differ and still be considered "more related".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-6, 10-11, and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Joachim et al. ("Analysis of Autoantibody Repertoires in Patients with Glaucoma," Meeting Abstract, Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA, May 5-10, 2002, Applicant's Information Disclosure statement).

Joachim et al. teach a method in which autoantibodies against retinal antigens were detected in the sera of glaucoma patients and healthy subjects. The autoantibodies were detected and measured by Western blot and subsequently analyzed by multivariate statistical techniques and artificial neural networks. The staining patterns of autoantibodies for each individual was digitized, grouped together, and analyzed by multivariate statistical techniques and artificial neural networks. Joachim et al. further teach that a difference in the autoantibody patterns of patients with primary open angle glaucoma was observed relative to the patterns of healthy controls.

Although Joachim et al. do not specifically recite that the method is used to diagnose glaucoma, the teaching is anticipatory since Joachim et al. teach all active method steps recited in claim 1. With respect to the recitation in claim 1 that "if the pattern of said individual is more related to the pattern of glaucoma patients than to the pattern of healthy individuals, glaucoma is diagnosed", the reference is anticipatory because this conditional limitation does not require diagnosis of glaucoma unless the first part of the recitation applies. Since the reference teaches, for example, that OHT patients were *not* found to be statistically different from controls (and thus were not "more related" to the pattern of glaucoma patients), there is no requirement in this case that diagnosis of glaucoma be performed.

With respect to claims 2-3, Joachim et al. teach that autoantibodies were specific for *retinal antigens*.

With respect to claims 4-6 and 17, Joachim et al. teach that *serum* was analyzed for the presence of autoantibodies.

With respect to claim 16, Joachim et al. teach that the autoantibody patterns were digitized and subsequently analyzed by multivariate statistical techniques as claimed.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joachim et al. in view of Grus et al. ("Computer-supported analysis (MegaBlot) of allopurinol-induced changes in the autoantibody repertoires of rats suffering from experimental lens-induced uveitis" *Electrophoresis* **18** (1997) 516-519).

Joachim et al. is as discussed above, which teaches methods in which autoantibody patterns (repertoires) of patients with glaucoma are compared to those of normal controls. However, the reference is an abstract and fails to explicitly state what number of autoantibodies made up the patterns.

Grus et al. teach that normal sera contain complex repertoires of naturally occurring autoantibodies, such that pathogenetically relevant autoantibodies may be eclipsed by such natural autoantibodies (p. 516, left column). In order to address this problem, Grus et al. teach a multivariate approach a quantitative immunoblot technique ("Megablot") in which several hundred autoantigens are screened simultaneously for corresponding autoantibodies (see the abstract and p. 516, "Introduction," in particular). Grus et al. teach that this multivariate approach allows for a quantitative analysis of whether differences between groups are

statistically significant in disease (see in particular Figure 1; p. 517, right column, the second paragraph; and p. 518-519, "Discussion"), and may also be used to detect and monitor changes in the autoantibody repertoire during treatment.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the method of Grus et al, in which several hundred autoantigens are simultaneously screened, in order to allow for quantitative comparison of normal and glaucoma groups, to prevent naturally occurring autoantibodies from masking changes in pathogenetically relevant ones, and/or to allow for monitoring of changes in pathogenetically relevant autoantibodies during treatment of glaucoma.

12. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Joachim et al. in view of Maruyama et al. ("Clinical Roles of Serum Autoantibody against Neuron-Specific Enolase in Glaucoma Patients" *Tohoku J. Exp. Med.* (July 2002), **197**, 125-132).

Joachim et al. is as discussed above, which teaches detecting and comparing autoantibody patterns in glaucoma. However, the reference fails to specifically teach that changes in autoantibody patterns over time were used to assess the progression and/or severity of glaucoma.

Maruyama et al. teach detection of an autoantibody against a retinal antigen (autoantibody against neuron-specific enolase), in which the autoantibody titers in glaucoma patients with and without visual field deterioration were compared in order to evaluate the clinical role of the autoantibody in relation to clinical findings (see in particular the abstract; p. 126, right column, the first full paragraph; p. 130, left column, the first paragraph). Glaucoma with visual field deterioration would be considered to be more severe than glaucoma without

such deterioration. Maruyama et al. found that the autoantibody titers were relatively higher in glaucoma with visual field deterioration than in patients without it (see also p. 131, left column). In addition, Maruyama et al. found that the autoantibody titers were observed to change with advancing glaucoma stages and/or deteriorating glaucomatous visual field losses (p. 130, left column and Figure 2). Maruyama et al. conclude that detection of the autoantibody may be used in diagnosis and to monitor glaucoma progression (p. 131, right column).

Therefore, it would have been obvious to one of ordinary skill in the art to assess changes in autoantibody patterns over time, as taught by Maruyama et al., in the method of detecting autoantibody patterns of Joachim et al. in order to monitor glaucoma progression. One would have a reasonable expectation of success because Maruyama et al. found that levels of one retinal autoantibody changed with glaucoma severity and with disease progression; and retinal autoantibodies were those studied in Joachim et al.

Response to Arguments

13. With respect to the status of claim 15, which was previously withdrawn by the Examiner as not reading on the elected species of "Western blot assay", Applicant argues that the claim should be examined because it recites "conventional electrophoretic techniques", of which "Western blot assay" is an example (Applicant's response, p. 6).

In the restriction requirement of record, Applicant was given the opportunity to elect **either** "Western blot assay" as in claims 10-11 **or** "electrophoretical techniques" as in claim 15 as species of methods of detection (see p. 4 of the Office action mailed 4/26/06, part b). Applicant elected "Western blot assay" in the response filed 5/12/06 and did not distinctly and

specifically point out the supposed errors in the restriction requirement. Accordingly, in the absence of a timely traversal, "electrophoretical techniques" is a non-elected species and claim 15 has been properly withdrawn because it does not read on the elected species.

Furthermore, the Examiner notes that claim 15 does not recite simply detection by "conventional electrophoretic techniques," but rather recites a multi-step detection method that involves binding autoantibodies to beads followed by "conventional electrophoretic techniques". This multi-step detection method not describe detection by Western blot assay and therefore cannot be said to read on the elected species.

14. With respect to the rejections of claims 1-11 and 16-18 under 35 USC 112, 1st paragraph (scope of enablement), Applicant argues that one of ordinary skill in the art would be able to practice the invention with body fluids other than serum (Applicant's response, p. 6-7).

Applicant has submitted four publications contended to demonstrate that antibodies may be found in other types of body fluids. Applicant also argues that the Baldas et al. reference, cited by the Examiner in the rejection, shows that antibodies can be found in saliva as well as serum. Regarding the publications submitted, Applicant states that the Torun et al. reference demonstrates that analysis of antibodies in aqueous humor is superior when compared to serum for diagnosis of toxoplasmosis (see English abstract on p. 110 of the publication). Similarly, Applicant argues that Kijlstra et al., Liekfeld et al. and Grus et al. show that antibodies can be found in aqueous humor and tears, in addition to in serum.

Applicant's arguments and the references have been fully considered by the Examiner but they are not found persuasive because the scope of the teaching in the references is not commensurate with the scope of the claimed invention. The claimed invention is directed to a

method for diagnosing glaucoma based on detection of autoantibodies against ocular antigens. None of the references submitted are directed to diagnosis of glaucoma. Furthermore, the Kijlstra et al. and Liekfeld et al. references do not relate to detection of autoantibodies against ocular antigens as claimed, but rather to detection of antibodies against *pathogens*. The fact that other body fluids may have antibodies is not a showing that is commensurate in scope with the claims. Furthermore, the references submitted relate to saliva, aqueous humor, and tears. The claims are not restricted to these body fluids, also including, for example, urine as claimed in claim 4.

The record shows that the prior art recognizes unpredictability in carrying out diagnosis based on measurements of antibodies in different types of body fluids (see the above rejection). Even if a particular body fluid harbors antibodies, detection of the antibodies in that fluid is not necessarily useful for diagnosis, as taught in Baldas et al. Applicant argues that the teachings of Baldas et al. cannot be generalized between different diseases (Applicant's response, see the paragraph bridging p. 6-7), but has not submitted any evidence or reasoning to this effect. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Applicant has also not submitted evidence as to why, in the case of glaucoma, one skilled in the art would expect to predictably extrapolate the specification's teachings of serum to other body fluids, given that the prior art recognizes that antibody measurements cannot be predictably extrapolated for all diseases.

Thus, in light of all the evidence of record, the Examiner maintains that the specification teachings relating to serum-based diagnosis are insufficient to predictably enable one skilled in the art to carry out diagnosis of glaucoma by detecting autoantibodies against ocular antigens in body fluids other than serum.

15. With respect to the rejections of claims 1-6, 10-11 and 16-17 under 35 USC 102(b) as being anticipated by Joachim et al., Applicant's arguments have been fully considered but they are not persuasive (see p. 6). Applicant argues that the reference is an abstract which gives general hints, but no proper working conditions. This argument is not found persuasive because the reference fully discloses all of the claim limitations, and is presumed to be operable/enabling in the absence of a submission of facts rebutting this presumption. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980).See MPEP 2121.

Applicant further argues that Joachim et al. fails to specifically teach a method of diagnosis of glaucoma as claimed. This argument is not found persuasive because as discussed in the above rejection, the recited step to which Applicant points is not required to be performed in the method; since the step is conditional the reference need not teach the step in order to anticipate the claim.

16. With respect to the rejections of claims 7-9 under 35 USC 103(a) as being unpatentable over Joachim et al. in view of Grus et al., Applicant argues that the Grus et al. reference deals with uveitis rather than glaucoma and that Grus et al. is not used for diagnostic purposes, but rather to monitor the influence of treatment, such that the claimed invention is not obvious (see p. 8-9). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The fact that Grus et al. relates to a different disease is not relevant since this feature is taught in the Joachim reference. The Examiner maintains that one skilled in the art would be motivated to simultaneously screen

several hundred autoantigens, as taught by Grus et al., in the method of Joachim et al. in order to allow for quantitative comparison of normal and glaucoma groups, for example. This system for simultaneous screening of autoantigens is would be particularly pertinent to the problem at hand, namely, the detection and analysis of complex patterns of autoantibody repertoires in Joachim et al.

17. With respect to the rejection of claim 18 under 35 USC 103(a) as being unpatentable over Joachim et al. in view of Maruyama et al., Applicant argues that one skilled in the art would conclude from the Maruyama et al. reference that the determination of single autoantibody (against NSE) is not suitable for diagnosis of glaucoma (p. 9). Applicant's arguments have been fully considered but they are not persusive.

First, Applicant's assertion that one skilled in the art would conclude that NSE antibody titers would not useful in a method for diagnosis of glaucoma is unsupported by the evidence of record. The Maruyama et al. reference clearly teaches that "serum anti-NSE antibody...may be one of the useful factors for diagnosing early stages of [primary open angle glaucoma], and for monitoring glaucoma progression of [normal tension glaucoma]" (p. 131, right column).

Second, Applicant appears to conclude that since one skilled in the art reading the Maruyama et al. reference would not believe (as asserted above) that anti-NSE antibody titers are useful in diagnosis of glaucoma, one skilled in the art would not be motivated combine testing for a single antibody (to NSE) as in Maruyama et al. with the teachings of Joachim et al. However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what

the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, Maruyama et al. teach that autoantibody titers change over time with advancing glaucoma stages and/or progression of the disease. As such, the Examiner maintains that it would have been obvious to assess changes in autoantibody patterns over time as taught by Maruyama et al. in the method of Joachim et al. in order to monitor the progression of glaucoma.

Conclusion

18. No claims are allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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